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February 4, 2003

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Examiner  
United States Patent and Trademark Office  
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Our Ref.: DT-3073/43816.1

Re: Application No. 09/380,015  
in the name of Carsten Korth  
filed on August 23, 1999

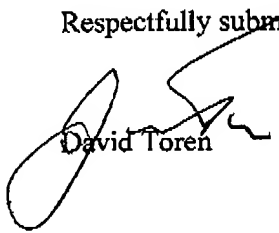
Dear Dr. Winkler:

Pursuant to your request and in preparation for the contemplated telephone conference on February 11, 2003 at 11:00 a.m., I am sending you "*Comments on Differences Between U.S. 5,846,533 (Prusiner) and 09/380,015 (Korth, et al.)*", including the *Nature* article mentioned in the comments.

You will note that the thrust of the comments is that the reference Prusiner did not in fact obtain antibodies capable to bind to PrP<sup>Sc</sup> and not to PrP<sup>C</sup>, as claimed in the present application.

On behalf of Dr. Moser, one of the inventors and Dr. Emmel, applicant's German patent attorney, we wish to thank you for making yourself available for the telephone interview on February 11<sup>th</sup>.

Respectfully submitted,

  
David Toren

DT:bsw  
Enclosure

04. Februar 2003

**Comments on differences between  
US 5,846,533 (Prusiner) and 09/380015 (Korth et al)**

In these comments we want to make clear that Prusiner in fact did not obtain antibodies able to bind to PrP<sup>Sc</sup> and not to PrP<sup>c</sup> (as claimed by Korth). This may also be the reason that the Prusiner-patent does not include claims for such antibodies. The antibodies claimed in the Prusiner-patent are able to bind native PrP<sup>Sc</sup> in situ which does not exclude that they also can bind to native PrP<sup>c</sup>.

Figures 9 and figure 10 of the Prusiner-patent only show that the obtained antibodies bind with higher specificity to SHa PrP 27-30 than antibody 3F4 which is known to bind to denatured PrP.

In this context one should note that the selection of the Prusiner-antibodies was done by phage panning with only selecting those phages able to bind to SHa PrP 27-30 (i.e. digested PrP<sup>Sc</sup>). It is not surprising that such technique leads to antibodies which bind specifically to SHa PrP 27-30 but it was not shown that these antibodies are not able to bind to native PrP<sup>c</sup> which is exactly what Korth et al are claiming. From the definition given in column 9 lines 27 ff it appears that "binds specifically" in the Prusiner Patent means that antibodies bind better to native PrP<sup>Sc</sup> than to denatured fragments of PrP<sup>c</sup>. Moreover in the whole Patent only digested PrP<sup>Sc</sup> is used for the antibody studies which would not have been necessary if the antibodies had the ability to exclusively detect PrP<sup>Sc</sup> and not PrP<sup>c</sup>. Note also Figure 8 in the Prusiner patent showing detection of PrP<sup>Sc</sup> only after protease digestion of PrP<sup>c</sup>. Also immunoprecipitation (results shown in Figs 11 and 12) was only performed with protease treated material (not containing PrP<sup>c</sup>).

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In this connection it is referred to the third paragraph on page 33 of the present application. In this passage, results of immunoprecipitation assays are discussed. These assays (used non protease treated homogenates) showed that antibody 15B3 precipitated PrP only from PrP<sup>Sc</sup> containing homogenates and that the precipitated PrP actually was PrP<sup>Sc</sup> (the precipitated PrP was protease resistant).

Consequently it is our opinion that antibody 15B3 has characteristics which are unique. Applicants do not have any doubt that the desire to obtain such antibodies and their value may have been discussed prior to the filing date of the application but in fact it is their firm belief that they were the first to have such antibodies in hand. Applicants published the novel properties of antibody 15B3 in Nature (copy enclosed) and among prion experts there was no doubt that the properties of this antibody were novel. In fact antibodies detecting PrP<sup>Sc</sup> but not PrP<sup>C</sup> were long awaited in prion field, e.g. for their specific advantages in diagnostic applications. Such antibodies eliminate the need for protease treatment of tissue homogenates (destroying PrP<sup>C</sup>) prior to detection of PrP 27-30. Antibody 15B3 identifies PrP<sup>Sc</sup> directly in untreated homogenates. For comparison please see attached Figure.

In this connection one should additionally note that applicants used a technology for the production of antibodies which also appears to be novel. Applicants used knock-out mice (as described in the Prusiner-patent) and immunised them with recombinant PrP both in oxidised and reduced form. Subsequently the spleen was removed from the immunised mice and splenocytes recovered therefrom were fused with hybridoma cell lines. The antibodies produced by the hybridoma cells were then tested for their ability to bind to PrP<sup>Sc</sup> or PrP<sup>C</sup> respectively. It should be noted that also Prusiner tried to produce antibodies by using hybridoma cell lines obtained after immunisation of knock-out mice (however, in his case SHa PrP 27-30 and not recombinant PrP was used for immunisation) which did not lead to the

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desired results. It could be that the differences between the antibodies obtained by Prusiner and those obtained by the applicants could go back to the different methods of producing the antibodies (even if applicants at present are not able to explain why their method surprisingly led to e.g. AB 15B3).